Information Type:	Statistical Analysis Plan (SAP)

TITLE PAGE

Protocol Title: A phase IIIB, open label, long-term follow-up study to assess persistence of immune responses to GSK's HZ/su vaccine 4-7 years after primary vaccination; and immunogenicity and safety assessment of revaccination with 2 additional doses of HZ/su vaccine, administered 1-2 months apart, 6-8 years after primary vaccination of adults with renal transplant from study ZOSTER-041.

Study Number: 212340 (ZOSTER-073 EXT:041 Y4-10)

Compound Number: GSK 1437173A

Abbreviated Title: Long-term immunogenicity study of Herpes Zoster subunit vaccine (GSK 1437173A) and immunogenicity and safety assessment of revaccination with two additional doses in adults with renal transplant from study ZOSTER-041.

Sponsor Name: GlaxoSmithKline Biologicals SA (GSK)

Regulatory Agency Identifier Number(s)

Registry	**ID**
Registry name	Registry ID
Clintrials.gov	NCT04176939
EudraCT number	2019-001815-21
Investigational New Drug (IND) number	BB-IND 13879

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Version history

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
1.0	12 Mar 2024	Amendment 1 Final: 15 June 2020	Not Applicable	Original version
2.0	12 Mar 2024	Amendment 1 Final: 15 June 2020		
			Section 1.2: • Added immunogenicity summaries where Visit 1, Visit 2, and Visit 3 in the LTFU phase of ZOSTER-073 will also be presented as Day 1, Month 12, and Month 24,	• In accordance to the primary endpoint timepoints for public disclosure
			Section 3.1: • Added PPS(LTFU) as a population that elimination code 2060 is applicable to and clarified the type of elimination is Visit(s) only, as applicable	• Concomitant infections could occur in the LTFU phase which could impact immunogenicity assessments at a particular visit or visits
			Section 4.2: • Clarified the immunogenicity	• Clarification that

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			summaries of seropositivity rates, GMCs, and MGI of anti-gE antibody in the LTFU phase will not be provided by age and immunosuppressive therapy	summaries will no longer be provided by subgroup
			Section 4.2.2.1: • Added reference point for MGI • Added summaries of GMCs, MGI, and seropositivity in LTFU phase presented as Day 1, Month 12, and Month 24, in	• To clarify MGI reference point • To present as Day 1, Month 12, and Month 24 for protocol primary endpoint timepoints public disclosure
			Section 4.2.2.2 and Section 4.3.1.2.3: • Added Boxplots of anti-gE antibody concentrations will be displayed by visit.	• Visual representation of summary statistics
			Section 4.3.2.1: • Added Visit 3 Month 23 to pre-	• Clarification of visit

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			revaccination timepoints • Added summaries of suspected or biopsy proven allograft rejections and HZ cases from ZOSTER-041 last visit to ZOSTER-073 Day 1 • Added summary of HZ cases from ZOSTER-073 Day 1 to Visit 3 Month 24	associated with pre-revaccination • To ensure biopsy rejections are summarized across all phases of study • To ensure HZ cases are summarized across all phases of study
			Section 4.3.2.2: • Added summaries of non-serious unsolicited AEs, non-serious causally related unsolicited AEs. • Added summary of biopsy rejections from Dose 1 up to 12 months post last revaccination. • Added summary of causally related	• To separate non-serious from combined non-serious and serious unsolicited AE summaries • To cover an additional portion of the revaccination follow up phase. • Summary is needed for

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			fatal unsolicited AEs. • Added definition of allograft dysfunction • Removed number of doses followed by SAE summaries	public disclosure. • To clarify which creatinine values constitute allograft dysfunction • SAEs are captured throughout the study not just within 30 days so cannot attribute to a dose
			Section 4.4.2: • CCI [redacted]	• CCI [redacted]
			Section 4.6.1: • Changed from 2 to 3 immunosuppressive therapy subgroups. • Clarified immunogenicity	• Single classes to be separate from 2 class combinations.

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			summaries will not be provided by subgroups	
			Section 4.5.2.2: • Removed COVID severity and outcome, AEs potentially indicating COVID, COVID symptoms, and COVID additional assessment summaries and listings .	• Company guidance and requirements for COVID summaries changed so removed to keep in line with all other studies in pipeline.
			Section 4.5.3.1: • Removed text about biopsy rejection. • Added text about allograft dysfunction summaries and time points	• Text was already described in Section 4.3.2.2, removed to avoid duplication. • To clarify how the creatinine measurements will be displayed for allograft. dysfunction endpoints.

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			Section 4.5.3.4: • Added the timepoints in which the number of subjects with HZ episodes would be tabulated.	• To clarify multiple summaries will be provided based on study phase.
			Section 6.1.1 • Updates text to state enrollment by country will be presented as part of demographic summaries.	• Moved country to demography summaries to reduce table counts
			Section 6.1.2: • Removed text about visit specific medical history listings	• To clarify only one medical history listing will be provided
			Section 6.1.4: • Added the following indications to the medical history summaries: anti-viral treatment for HZ, pain rescue medication to control HZ pain,	• To include all medical indications on the CRF for concomitant medications.

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			and other therapy for HZ. • Moved sentence stating the duration of therapeutic immunosuppressive therapy will be displayed in the listing of concomitant medications from 6.5.3.1	• Applied to concomitant medications listing not other safety measurements.
			Section 6.1.3: • Added text stating not revaccinated subjects will be summarized with the protocol deviations resulting in exclusion.	• While not a protocol deviation per se, these subjects are eliminated from exposed set and PPS for revaccination active and follow-up phases.
			Section 6.1.4: • Added text that concomitant medication indications of Pain for HZ and other HZ meds will be displayed	• Clarified all indications will be displayed

SAP Version	Approval Date	Protocol Version (Date) on which SAP is Based	Change	Rationale
			Section 6.2.3: • Added text defining baseline and post baseline definitions in regards to rejection episodes, post-revaccination, and HZ episodes.	• To clarify how to handle multiple measurements for each type of summary.

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses to be included in the clinical study report (CSR) for Study 212340 (ZOSTER-073 EXT:041 Y4-10).

Details of the planned interim and final analyses are provided.

1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
LTFU phase - Immunogenicity assessment • To evaluate persistence of humoral immunity after primary vaccination course.	***In all subjects:*** • Anti-gE antibody concentrations as determined by ELISA at Day 1, Month 12, and Month 24.
Revaccination active phase - Immunogenicity assessment • To evaluate humoral immunity of HZ/su vaccine post-revaccination Doses 1 & 2.	***In all subjects:*** • Anti-gE antibody concentrations as determined by ELISA at pre-revaccination (Month 24) and at 1-month post-revaccination Dose 1 (Month 25) and Dose 2 (Month 26).
Secondary	
LTFU phase - Immunogenicity assessment • To evaluate persistence of cellular immunity after primary vaccination course.	***In CMI sub-cohort:*** • Frequencies of gE-specific CD4+ T-cells expressing two or more markers such as IFN-γ, IL-2, TNF-α, CD40L as determined by ICS at Day 1, Month 12, and Month 24.
LTFU phase - safety assessment • To evaluate safety of HZ/su vaccine from the study ZOSTER-041 last visit to study ZOSTER-073 Visit 3.	***In all subjects:*** • Related-SAEs – Occurrence of SAEs related to primary vaccination as assessed by the investigator from the study ZOSTER-041 last visit (Month 13) to study ZOSTER-073 Visit 3 (Month 24). • HZ episodes – Occurrence of suspected or confirmed HZ cases from the study ZOSTER-041 last visit (Month 13) to study ZOSTER-073 Visit 1 (Day 1). – Occurrence of confirmed HZ cases from Day 1 through Month 24. • AESIs – Occurrence of suspected or biopsy-proven allograft rejections from the study ZOSTER-041 last visit (Month 13) to study ZOSTER-073 Visit 1 (Day 1). – Occurrence of biopsy-proven allograft rejections from Day 1 through Month 24.

Objectives	Endpoints
	• Allograft function for episode(s) of allograft rejection. – Occurrence of allograft dysfunction through assessment of all clinically obtained serum creatinine measures from 2 months prior to an episode of biopsy-proven rejection and up to 2 months after rejection resolution and cessation of therapeutic immunosuppressive therapy for the time period from study ZOSTER-041 last visit (Month 13) to study ZOSTER-073 Visit 3 (Month 24). • Allograft function for episode(s) of HZ – Occurrence of allograft dysfunction through assessment of all clinically obtained serum creatinine measures from 2 months prior to an episode of HZ and up to 2 months after HZ rash resolution for the time period from study ZOSTER-041 last visit (Month 13) to study ZOSTER-073 Visit 3 (Month 24).
<u>Revaccination active phase - Immunogenicity assessment</u> • To evaluate cell-mediated immunity post- revaccination Doses 1 & 2.	***In revaccinated subjects in CMI sub-cohort:*** • Frequencies of gE-specific CD4+ T-cells expressing two or more markers such as IFN-γ, IL-2, TNF-α, CD40L as determined by ICS at pre-vaccination (Month 24) and at 1-month post-revaccination Dose 1 (Month 25) and Dose 2 (Month 26).
<u>Revaccination follow-up phase – Immunogenicity assessment</u> • To evaluate persistence of humoral and cell-mediated immune responses post-revaccination Dose 2.	***In all revaccinated subjects:*** • Anti-gE antibody concentrations as determined by ELISA at 12 months and 24 months post-revaccination Dose 2. ***In revaccinated subjects in CMI sub-cohort:*** • Frequencies of gE-specific CD4+ T- cells expressing two or more markers such as IFN-γ, IL-2, TNF-α, CD40L as determined by ICS at 12 months and 24 months post-revaccination Dose 2 in a CMI sub-cohort of subjects.
<u>Revaccination active and follow-up phases - Safety assessment</u> • To evaluate reactogenicity and safety of the HZ/su vaccine after each revaccination.	***In all revaccinated subjects:*** • Solicited local and general AEs: – Occurrence, duration, and intensity of solicited local AEs within 7 days after each revaccination (i.e., the day of revaccination and 6 subsequent days); – Occurrence, duration, and intensity of solicited general AEs within 7 days after each revaccination dose (i.e., the day of revaccination and 6 subsequent days) and causal relationship to revaccination by investigator assessment. • Unsolicited AEs

Objectives	Endpoints
	– Occurrence, intensity of unsolicited AEs during 30 days after each revaccination (i.e., the day of revaccination and 29 subsequent days) and causal relationship to revaccination by investigator assessment. • SAEs – Occurrence of SAEs (including fatal SAEs) from Dose 1 of revaccination (Month 24) until 12 months post-last revaccination dose (Month 37). – Occurrence of related-SAEs (including related-fatal SAEs) as per investigator assessment from Dose 1 of revaccination (Month 24) up to study end (Month 49). • AESIs – Occurrence of all biopsy-proven allograft rejections from Dose 1 of revaccination (Month 24) up to study end (Month 49) and causal relationship to revaccination by investigator assessment. – Occurrence of pIMDs from Dose 1 of revaccination (Month 24) up to 12 months post-last revaccination dose (Month 37) and causal relationship by investigator assessment. • HZ episodes – Occurrence of confirmed HZ cases from Dose 1 of revaccination (Month 24) up to study end (Month 49). • Allograft function following revaccination – Occurrence of allograft dysfunction through assessment of all clinically obtained serum creatinine measures from 3 months before the first revaccination dose until 3 months after the last revaccination dose. • Allograft function for episode(s) of allograft rejection – Occurrence of allograft dysfunction through assessment of all clinically obtained serum creatinine measures from 2 months prior to an episode of biopsy-proven rejection and up to 2 months after rejection resolution and cessation of therapeutic of immunosuppressive therapy. • Allograft function for episode(s) of HZ – Occurrence of allograft dysfunction through assessment of all clinically obtained serum creatinine measures from 2 months prior to an episode of HZ and up to 2 months after HZ resolution.

Objectives	Endpoints
Tertiary	
CCI	

CMI = Cell-Mediated Immunity; CCI **ELISA** = Enzyme Linked Immunosorbent Assay; **gE** = glycoprotein E; CCI **ICS** = Intracellular Cytokine Staining; **IL-2** = Interleukin 2; CCI **TNFα** = Tumor Necrosis Factor-alpha; **IFNγ** = Interferon-gamma; **AE** = Adverse Event; **SAE** = Serious Adverse Event; **HZ** = Herpes Zoster**; AESI** = Adverse Event of Special Interest; **pIMDs** = potential Immune-Mediated Diseases.
*To be performed by a central laboratory if deemed necessary

1.2. Study Design

This study will evaluate the persistence of gE-specific immunogenicity after the primary 2-dose HZ/su vaccination in study ZOSTER-041 and the effect on immunogenicity and safety of revaccination with two additional doses of HZ/su vaccine after approximately 7 years in ZOSTER-041 in renal transplant (RT) subjects taking daily chronic immunosuppressive (CIS) therapy. Former study ZOSTER-041 subjects who received two doses of HZ/su vaccine were offered enrollment into study ZOSTER-073 at participating centers.

This study has three distinct phases:

- In the long-term follow-up (LTFU) phase, subjects will be followed for two years* (Day 1 to Month 24) in ZOSTER-073 study, which is approximately 4-7 years since primary vaccination in ZOSTER-041 study. Over the same time period, the occurrence of confirmed HZ cases and biopsy-proven RT rejections will be prospectively collected. Whereas the occurrence of confirmed/suspected HZ cases; and RT rejections, during the gap between studies ZOSTER-041 and ZOSTER-073, will be retrospectively collected back to subjects' study ZOSTER-041 last visit.

  ** Subjects who are ineligible for revaccination or unwilling to receive revaccination (hereafter referred to as non-revaccinated subjects) will be invited to be followed in an extension of the LTFU phase for a total of 4 years (Day 1 to Month 49) in ZOSTER-073 study, which is approximately 8-11 years since primary vaccination series in ZOSTER-041 study, with safety and immunogenicity assessments at study Months 37 and 49.*

- In the revaccination active phase (study Months 24 through 26), subjects will receive two additional doses of HZ/su vaccine, administered on a 1 to 2-month apart schedule at study Months 24 and 25. Safety and immunogenicity assessments will be performed 1 month post-revaccination Doses 1 and 2 at study Months 25 and 26, respectively.
- In the revaccination follow-up phase (study Month 26 to study end), safety and immunogenicity following revaccination will be prospectively monitored at study Months 37 and 49 (i.e., 12 and 24 months post-revaccination Dose 2).

Overview of Study Design
HZ/su = Herpes zoster subunit; LTFU = Long-term follow-up; Vacc 1-2 = Vaccination dose 1 & 2; re-Vacc 1-2 = Revaccinations dose 1 & 2 *The second dose of revaccination (Visit 4, study Month 25) will be administered 1 to 2 months after the first revaccination dose. **Visit 5 (study Month 26), Visit 6 (study Month 37) and Visit 7 (study Month 49) will occur 1, 12 and 24 months after the second revaccination, respectively. $Phone contact will occur about 35 days before Visit 3 (study Month 24) to remind female subjects of childbearing potential to use adequate contraception.

Overview of Study Design Key Features	
Design Features	• **Type of study:** extension of other protocol(s); ZOSTER-041 for the analysis of long-term immunogenicity and safety. • **Experimental design**: Phase IIIB, open-label, uncontrolled, multi-centric, single group study. • **Duration of the study:** The study duration per subject will be approximately 49 months. – Epoch 001: LTFU phase starting at Visit 1 (Day 1) and ending at Visit 3 (study Month 24) – Epoch 002: Revaccination phase starting at Visit 3 (study Month 24) and ending at Visit 7 (study Month 49) • **Primary completion Date (PCD):** Visit 5 (study Month 26). The date that the final subject was examined or received an intervention for the purpose of final collection of data for all primary outcomes, whether the clinical trial was concluded according to the pre-specified protocol or was terminated • **End of Study (EoS):** Last testing results released of samples collected up to Visit 7 (study Month 49). • **Study group:**

Table 1 Study group, treatment, and epochs in the study

Study groups*	Target Number of subjects	Actual Number of subjects	Age (Min-Max)**	Treatment name	Epochs	
	From ZOSTER-041 primary study				Epoch 001 (open)	Epoch 002 (open)
HZ/su	86	68	20 years - 82 years	HZ/su	•	•

HZ/su = Herpes Zoster subunit vaccine.
*HZ/su Group name for subjects who were vaccinated with 2 doses of HZ/su in study ZOSTER 041.
**Age at the first vaccination in study ZOSTER-041.

- **Control**: uncontrolled.
- **Revaccination schedule**: Subjects will receive two additional doses of the HZ/su vaccine, at Visit 3 (study Month 24) and at Visit 4 (study Month 25) in the revaccination phase.
- **Treatment allocation:** All eligible subjects will be enrolled into HZ/su group.
- **Blinding:** Open-label.
- **Sampling schedule**:
  - Blood samples to assess humoral immunogenicity will be collected from all subjects at Visit 1 (Day 1), Visit 2 (study Month 12), Visit 3 (study Month 24), Visit 4 (study Month 25)*, Visit 5 (study Month 26)*, Visit 6 (study Month 37) and Visit 7 (study Month 49).
  - Blood samples to assess CMI responses will be collected in the CMI sub-cohort at Visit 1 (Day 1), Visit 2 (study Month 12), Visit 3 (study Month 24), Visit 4 (study Month 25)*, Visit 5 (study Month 26)*, Visit 6 (study Month 37) and Visit 7 (study Month 49).
  - CCI [redacted]

  **Blood samples will not be collected at Visit 4 (*study *Month 25) and Visit 5 (*study *Month 26) from non-revaccinated subjects.*
  - Clinical specimens of HZ lesions (from 3 separate lesions) will be collected from subjects clinically diagnosed as having a suspected case of HZ.

Overview of Study Design Key Features	
	– A urine sample (blood sample only if required by country, local or ethics committee regulations) will be collected from all female subjects of childbearing potential before revaccination at Visit 3 (study Month 24) and Visit 4 (study Month 25) for pregnancy testing. • **Data collection**: electronic Case Report Form (eCRF). – Solicited and unsolicited AEs will be collected using a subject Diary (paper Diary) and transcribed into eCRF. – In the event of suspected HZ, the HZ clinical course will be collected using a HZ-specific Diary and Zoster Brief Pain Inventory (ZBPI) questionnaire and transcribed into eCRF. • **Safety monitoring**: An internal safety review team (SRT, study team members) will review available safety data on a regular basis throughout the study. Any potential safety concern identified will be escalated to higher governing bodies as per internal GSK process.

Note: all ZOSTER-073 visits that are part of the LTFU phase (for both revaccinated and non-revaccinated subjects) will be displayed in terms of time since ZOSTER-041 primary vaccination series, which will be presented in 1 year intervals.

Since the interval between the end of ZOSTER-041 study and the start of this ZOSTER-073 study will vary per subject and is dependent on receipt of approval or implementing the study in the different participating countries, some results from the first ZOSTER-073 blood sample may correspond to year 4, year 5, or year 6 post vaccination. To be able to complement the modelling prediction by descriptive data analysis, yearly timeframes will be defined around the anniversary date post vaccination. The details of the set up for these intervals is described below.

The timeframe of first visit of the ZOSTER-073 study in LTFU phase will be computed between the date of the first visit of ZOSTER-073 study and the administration date of the second dose of primary series vaccination in the ZOSTER-041 study.

Time frame of first visit= (date of the first visit of ZOSTER-073 - date of vaccination dose 2 in ZOSTER-041+1) /365

The result of the first visit will be assigned to each yearly timeframe derived as follow

Timeframe of first visit	Lower bound of timeframe of first visit	Upper bound of timeframe of first visit
4	[3.5	<4.5)
5	[4.5	<5.5)
6	[5.5	<6.5)
The brackets indicate inclusive.		

Yearly timeframe for the persistence analysis in the LTFU phase will be calculated by adding 1 year to the timeframe of first visit for each subsequent visit.

Example

	Primary series dose 2 – ZOSTER-041	**Day 1-ZOSTER-073 Blood sample**	**time since primary series dose 2**	**assigned time frame for the ZOSTER-073 Visit 1 Day 1 blood sample**	**assigned time frame for the ZOSTER-073 Visit 2 blood sample**	**assigned time frame for the ZOSTER-073 Visit 3 blood sample**
subject 1	1-nov-11	2-feb-16	4.260273973	4	5	6
subject 2	1-nov-11	5-jul-16	4.682191781	5	6	7

Similar computations will be performed for ZOSTER-073 Visit 6 and Visit 7 for non-revaccinated subjects.

Since pre-revaccination visits encompass a broad time range post-dose 2 of the primary series, the same interval may include one subject's data from ZOSTER-073 Visit 1 and another subject's Visit 2 data due to overlapping in timepoints by study year associated with the long-term follow-up phase.

Timepoints from ZOSTER-041 will be displayed in the immunogenicity summaries for both the LTFU phase and revaccination active and follow-up phases.

The following visits will appear in the immunogenicity summaries for the Per Protocol Set for analysis of persistence (LTFU phase). ZOSTER-041 Visits 1-5 and ZOSTER-073 Visits 1-3 will include data from both revaccinated and non-revaccinated subjects (prior to revaccination). ZOSTER-073 Visit 6 and Visit 7 will include data from non-revaccinated subjects only.

Study Phase	**Subjects**	**Visit Number**	**SDTM.IS Visit Number**	**Study Month**	**Display**	**Description**
ZOSTER-041	Revaccinated and Non-revaccinated	Visit 1	10	Month 0	PRE	Pre-vaccination (Month 0)
		Visit 2	20	Month 1	PI(M1)	Post-vaccination dose 1 (Month 1) – 1 month post-dose 1 ZOSTER-041

		Visit 3	30	Month 2	PII(M2)	Post-vaccination dose 2 (Month 2) – 1 month post-dose 2 ZOSTER-041
		Visit 4	50	Month 7	PII(M7)	Post-vaccination dose 2 (Month 7) – 6 months post-dose 2 ZOSTER-041
		Visit 5	70	Month 13	PII(M13)	Post-vaccination dose 2 (Month 13) – 12 months post-dose 2 ZOSTER-041
LTFU	Revaccinated and Non-revaccinated	Visit 1	10	Day 1	4YPD2 5YPD2 6YPD2 7YPD2 8YPD2 …	XYPD2= X years Post-vaccination dose 2 - from X.X up to less than X.X years post-vaccination dose 2 ZOSTER-041
		Visit 2	20	Month 12		
		Visit 3	30	Month 24		
	Non-revaccinated only	Visit 6	60	Month 37		
		Visit 7	70	Month 49		

Visit 1, Visit 2, and Visit 3 in the LTFU phase of ZOSTER-073 will also be presented as Day 1, Month 12, and Month 24, in accordance to the endpoint timepoints.

The following visits will appear in the immunogenicity summaries for the Per Protocol Set for immunogenicity after revaccination. Only data for revaccinated subjects will be included at all timepoints.

Study Phase	**Subjects**	**Visit Number**	**SDTM.IS Visit Number**	**Study Month**	**Display**	**Description**
ZOSTER-041	Revaccinated only	Visit 1	10	Month 0	PRE	Pre-vaccination (Month 0)
		Visit 2	20	Month 1	PI(M1)	Post-vaccination dose 1 (Month 1) – 1 month post-dose 1 ZOSTER-041
		Visit 3	30	Month 2	PII(M2)	Post-vaccination dose 2 (Month 2) – 1 month post-dose 2 ZOSTER-041

		Visit 4	50	Month 7	PII(M7)	Post-vaccination dose 2 (Month 7) – 6 months post-dose 2 ZOSTER-041
		Visit 5	70	Month 13	PII(M13)	Post-vaccination dose 2 (Month 13) – 12 months post-dose 2 ZOSTER-041
LTFU	Revaccinated only	Visit 1	10	Day 1	4YPD2 5YPD2 6YPD2 7YPD2 8YPD2 …	XYPD2= X years Post-vaccination dose 2 - from X.X up to less than X.X years post-vaccination dose 2 ZOSTER-041
		Visit 2	20	Month 12		
		Visit 3	30	Month 24		
Revaccination active	Revaccinated only	Visit 3*	30	Month 24	PRE-RV	Pre-Revaccination baseline
		Visit 4	40	Month 25	1MPR1	Post-Revaccination Dose 1 (Month 1) 1 month post-revaccination 1
		Visit 5	50	Month 26	1MPR2	Post-Revaccination Dose 2 (Month 2) 1 month post-revaccination 2
Revaccination Follow-up	Revaccinated only	Visit 6	60	Month 37	12MPR2	Post-Revaccination Dose 2 (Month 13) 12 months, or 1 year, post-revaccination 2
		Visit 7	70	Month 49	24MPR2	Post-Revaccination Dose 2

						(Month 25) 24 months, or 2 years, post-revaccination 2

*If Visit 3 assessments are not available, Visit 2 or Visit 1 could be used as pre-revaccination baseline is the latest pre-revaccination dose assessment with a non-missing result from ZOSTER-073.

2. STATISTICAL HYPOTHESES

2.1. Hypothesis testing

All statistical analyses will be descriptive. No formal hypothesis testing will be conducted.

2.2. Multiplicity Adjustment

No statistical adjustment will be made for the interim or final analysis, which is intended to provide descriptive outputs in a phased manner, according to the relevant endpoint timepoints.

3. ANALYSIS SETS

Analysis Set	Description
Enrolled Set	All subjects with a complete vaccination course (2 doses of HZ/su vaccine) in study ZOSTER-041 who met the eligibility criteria and signed informed consent in the study ZOSTER-073.
Per Protocol Set (PPS) for analysis of persistence (LTFU phase from Visit 1 to Visit 3 for all subjects, and at Visit 6 and Visit 7 for non-revaccinated subjects)	The PPS for analysis of persistence will include evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures and intervals defined in the protocol, with no elimination criteria) from the Enrolled Set for whom any persistence immunogenicity endpoints measures after primary vaccination course are available from Visit 1 (Day 1) to Visit 3 (study Month 24) regardless of revaccination status and at Visit 6 (study Month 37) and/or Visit 7 (study Month 49) for non-revaccinated subjects.
Exposed Set (ES) for revaccination phase	The ES for analysis of safety will include all subjects with at least one HZ/su vaccine dose administered in the study ZOSTER-073.
PPS for Immunogenicity after revaccination course (revaccination active phase)	The PPS for analysis of immunogenicity after revaccination will be defined by time-point and will include evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures and intervals defined in the protocol, with no elimination criteria) from the **ES for revaccination** who have received 1 or 2 doses of revaccination up to the time point considered from Visit 3 (study Month 24) to Visit 5 (study Month 26) (i.e. 1 dose for Visit 4 and 2 doses for Visit 5) and have any immunogenicity endpoint measures available.
PPS for persistence after revaccination course (revaccination follow-up phase)	The PPS for persistence for analysis of immunogenicity after revaccination will include evaluable subjects (i.e. those meeting all eligibility criteria, complying with the procedures and intervals defined in the protocol, with no elimination criteria) from the ES for revaccination who received 2 doses of revaccination for whom persistence immunogenicity endpoints measures after revaccination course are available with any immunogenicity endpoint measures available from Visit 6 (study Month 37) to Visit 7 (study Month 49).

An adapted PPS for Immunogenicity after revaccination (revaccination active and follow-up phases) will be used in the tables to present revaccination Visits 3-7 together. The Enrolled Set will be used for LTFU phase safety analyses. For non-revaccinated subjects, the Enrolled Set will be used for analyses of safety and the PPS for analysis of persistence will be used for analyses of immunogenicity.

3.1. Criteria for eliminating data from analysis sets

Elimination codes are used to identify subjects to be eliminated from analysis due to various conditions.

Code	Condition under which the code is used	Analysis set eliminated from	Visit (timepoints) where the code is applicable	Type of Elimination
800	Fraudulent data	All	Visit 1 – Visit 7	Eliminate from all Visits
900	Invalid ICF	All	Visit 1 – Visit 7	Eliminate from all Visits
900	Subject and investigator signed informed consent never available on site	All	Visit 1 – Visit 7	Eliminate from all Visits
900	Wrong informed consent version signed, and never re-consented with correct version prior to revaccination	All	Visit 1 – Visit 7	Eliminate from all Visits
900	Informed consent never signed and/or dated by subject	All	Visit 1 – Visit 7	Eliminate from all Visits
900	Informed consent never signed and/or dated by appropriate site staff.	All	Visit 1 – Visit 7	Eliminate from all Visits
900	Other informed consent violation that cannot or were not corrected under GCP	All	Visit 1 – Visit 7	Eliminate from all Visits
1030	Study vaccine not re-administered	ES, PPS (revacc. active phase), PPS (revacc. follow-up phase)	Visit 3 – Visit 7	Eliminate from Visit and onwards
1040	Administration of concomitant vaccine(s) forbidden in the protocol	PPS (LTFU), PPS (revacc. active phase), PPS (revacc. follow-up phase)	Visit 1 – Visit 7	Eliminate from Visit and onwards
1070	Study vaccine administration route not according to protocol i.e., Subjects that received multiple doses at 1 visit, subjects whose route of vaccination is not IM Injection, or wrong reconstitution. Note that laterality is preferred but not required, therefore vaccine administration in non-dominant arm will be included in analysis.	PPS (revacc. active phase), PPS (revacc. follow-up phase)	Visit 3 – Visit 7	Eliminate from Visit and onwards
1080	Vaccine temperature deviation or vaccine administered despite poor Good Manufacturing Practices (GMP)	PPS (revacc. active phase), PPS (revacc. follow-up phase)	Visit 3 – Visit 7	Eliminate from Visit and onwards
1090	Expired vaccine administered to subject	PPS (revacc. active phase), PPS (revacc. follow-up phase)	Visit 3 – Visit 7	Eliminate from Visit and onwards
2010	Protocol violation (inclusion/exclusion criteria) – Ineligible subject was	PPS (revacc. active phase), PPS	Visit 3 – Visit 7	Eliminate from Visit and onwards

Code	Condition under which the code is used	Analysis set eliminated from	Visit (timepoints) where the code is applicable	Type of Elimination
	revaccinated without fulfilling the eligibility criteria for revaccination	(revacc. follow-up phase)		
2040	Administration of any concomitant medication(s) forbidden by the protocol	PPS (revacc. active phase), PPS (revacc. follow-up phase)	Visit 1 – Visit 7	Eliminate from Visit(s) only, as applicable
2050	Underlying medical condition forbidden by the protocol, or some Intercurrent medical conditions (IMCs). (To be determined before analysis during data management review (DMR))	PPS (LTFU), PPS (revacc. active phase), PPS (revacc. follow-up phase)	Visit 1 – Visit 7 (visit and onward)	Eliminate from Visit and onwards
2060	Concomitant infection related to the revaccination which may influence immune response – For example, clinically diagnosed suspected HZ cases before Visit 1 or PCR confirmed HZ cases after Visit 1	PPS (LTFU), PPS (revacc. active phase), PPS (revacc. follow-up phase)	Visit 1 – Visit 7	Eliminate from Visit(s) only, as applicable
2070	Concomitant infection not related to the vaccine which may influence immune response – For example, in case of revaccination, any additional confirmed or suspected immunosuppressive or immunodeficient condition (e.g., malignancy, hepatitis, HIV infection, systemic infection)	PPS (LTFU), PPS (revacc. active phase), PPS (revacc. follow-up phase)	Visit 1 – Visit 7	Eliminate from Visit and onwards
2080	Out of window treatment administration – Revaccination dose 1 (study Month 24) to revaccination dose 2 (study Month 25) outside 25-90 day interval	PPS (revacc. active phase), PPS (revacc. follow-up phase)	Visit 3 – Visit 4	Eliminate from Visit and onwards
2090	Missed Visit, excluding phone contact *Note*: this does not apply to delayed enrolled subjects who had their Visit 1 and Visit 2 on the same day.	PPS (LTFU), PPS (revacc. active phase), PPS (revacc. follow-up phase)	Visit 1 – Visit 7	Eliminate from Visit only
2090	Assessment not properly performed – For example, incomplete assessment, missed assessment except safety follow-up *Note*: this does not apply to delayed enrolled subjects who had their Visit 1 and Visit 2 on the same day. These subjects would have to have an assessment at *either* Visit 1 or Visit 2.	PPS (LTFU), PPS (revacc. active phase), PPS (revacc. follow-up phase)	Visit 1 – Visit 7	Eliminate from Visit only

Code	Condition under which the code is used	Analysis set eliminated from	Visit (timepoints) where the code is applicable	Type of Elimination
2090	Number of days between Visit 3 and Visit 4 blood sample is outside [25-90 days]	PPS (revacc. active phase), PPS (revacc. follow-up phase)	Visit 3 – Visit 4	Eliminate from Visit only
	Number of days between Visit 4 and Visit 5 blood sample is outside [25-90 days]	PPS (revacc. active phase), PPS (revacc. follow-up phase)	Visit 4 – Visit 5	Eliminate from Visit only
2100	Serological results not available or blood sample not enough (low volume, not sufficient to perform testing).	PPS (LTFU), PPS (revacc. active phase), PPS (revacc. follow-up phase)	Visit 1 – Visit 7 Note: only the timepoint of the missing result will be excluded. For example, if a subject is missing results from Visit 1, but has results from other timepoints, only the Visit 1 will be excluded, the results at the other timepoints will be presented.	Eliminate from Visit only
2120	Assessment not properly performed – Obvious incoherence or abnormality or error in data, or unreliable data as a result of confirmed sample mismatch or confirmed inappropriate sample handling (including temperature deviations of samples) at lab	PPS (LTFU), PPS (revacc. active phase), PPS (revacc. follow-up phase)	Visit 1 – Visit 7	Eliminate from Visit only
2500	Vaccinated but lower volume was given	PPS (revacc. active phase), PPS (revacc. follow-up phase)	Visit 3 - Visit 7	Eliminate from Visit and onwards

Prior to database lock, during data management review (DMR), it will be determined if an elimination code applies to all visits, a specific visit (timepoint) only, or a specific visit (timepoint) onwards.

The investigator should endeavour to have the subjects come in for the visits within the protocol defined intervals, however, subjects may not be excluded from the PPS for Immunogenicity after revaccination course if they make the study visit outside these intervals. The intervals between study visits may not match the protocol defined and amended time windows due to special circumstances in which case, at the discretion of the sponsor, the

intervals may be extended to the below intervals for analysis. These new windows will be used in determining PPS elimination as part of code 2090.

Visit	**Original Protocol Defined Intervals**	**Amended Protocol Intervals allowed during special circumstances (e.g., COVID-19 pandemic)**	**Intervals allowed for statistical analysis**
Visit 1 – Visit 2	[330-415 days]	Target: [180-540 days] *The start of the interval may be moved by up to 6 months (starting no later than 18 months post-Visit 1)*	Any interval as informative for LTFU
Visit 1 – Visit 3	[690-775 days]	*The start of the interval may be moved by up to 6 months (starting no later than 30 months post-Visit 1), e.g., to avoid potential seasonal recurrence of COVID-19.* [510-985 days] *For delayed enrolled subjects, there is no strict interval. Ideally, there would be at least 6 months between their combined Visit 1/Visit 2 and Visit 3, but this is not required. The latest timepoint for Visit 3 to occur for delayed enrolled subjects would match the latest timepoint of all other previously enrolled subjects' Visit 3 so that all subjects can be revaccinated contemporaneously. The goal is to maintain similar revaccination follow-up*	Any interval as informative for LTFU

		timing so as not to delay study end.	
Visit 3 – Visit 4	[30-60 days]	[30-182 days]	[25-90* days]
Visit 4 – Visit 5	[30-48 days]	[30-90 days]	[25-90* days]
Visit 4 – Visit 6	[330-415 days]	[330-445 days] The allowed interval for Visits 6 should be the same for both the re-vaccinated and non-revaccinated subjects.	Any interval as informative for LTFU
Visit 4 – Visit 7	[690-775 days]	[690-805 days] *Visit 7 may be Scheduled earlier to make up for delays incurred during times of special circumstance, in order to maintain planned duration of the study. Delayed or cancelled if special circumstances preclude the original planned visit.* The allowed interval for Visit 7 should be the same for both the re-vaccinated and non-revaccinated subjects.	Any interval as informative for LTFU

Additionally, out-of-window visits are expected due to COVID-19 pandemic issues that do not fall into the “special circumstances” as just described, e.g., reduced clinic hours or patient capacity, but not the “clinics closed” requirement to enact special circumstances provisions. Determination of elimination, or not, for these out-of-window visits will take place during DMR pre-analysis.

Official elimination will take place during DMR in the pre-analysis meeting as the intervals for PPS eligibility may need to be adjusted or expanded further as the goal is to get as much immunogenicity and LTFU data as possible in this small sample size.

4. STATISTICAL ANALYSES

4.1. General Considerations

4.1.1. General Methodology

Confidence intervals (CIs) will use 95% confidence levels unless otherwise specified.

The exact confidence intervals around within-group proportions are derived using the method of Clopper and Pearson [Clopper, 1934].

Unless otherwise specified, continuous data will be summarized using descriptive statistics: n, mean, standard deviation (std), median, minimum, and maximum. Categorical data will be summarized as the number and percentage of subjects in each category.

4.1.2. Baseline Definition

For the LTFU phase, baseline is latest non-missing pre-primary series dose assessment from ZOSTER-041 study.

For the revaccination active and follow-up phases, baseline is the latest pre-revaccination dose assessment with a non-missing result from ZOSTER-073.

To assess long-term follow-up duration and decline post primary vaccination series peak-response, 1 month post-dose 2 of primary vaccination in ZOSTER-041 will be used.

Unless otherwise stated, if baseline data is missing, no derivation will be performed, and baseline will be set to missing.

4.2. Primary Endpoints Analyses

The primary immunogenicity analysis for the LTFU phase will be performed using the PPS for analysis of persistence (LTFU phase from Visit 1 to Visit 3 for all subjects, and at Visit 6 and Visit 7 for non-revaccinated subjects). If 5% subjects or more with serological results are eliminated from the PPS for analysis of persistence, then a complementary analysis will be performed on the Enrolled Set.

The primary immunogenicity analysis for the revaccination active phase will be performed on the PPS for immunogenicity after revaccination course (revaccination active phase). If 5% subjects or more with serological results are eliminated from the PPS for revaccination active phase, then a complementary analysis will be performed on the Exposed Set.

All analyses will be performed overall.

4.2.1. Definition of endpoints

GMC calculations will be performed by taking the anti-log of the mean of the log base 10 concentration transformations. The 95% CIs for GMC will be based on a back transformation of the student CI for the mean of the log-transformation. Antibody concentrations below the cut-off of the assay will be given an arbitrary value of half the cut-off for the purpose of GMC calculation. The cut-off for the anti-gE Ab assay is 97 mIU/ml.

The vaccine response rate (VRR) is defined as the percentage of subjects who has at least:

- a 4-fold increase in the post last vaccination anti-gE Ab concentration as compared to the pre-vaccination anti-gE Ab concentration for subjects who are seropositive at baseline.

  OR

- a 4-fold increase in the post last vaccination anti-gE Ab concentration as compared to the anti-gE Ab cut-off value for seropositivity for subjects who are seronegative at baseline.

A seropositive subject has an anti-gE Ab concentration is greater than or equal to the cut-off value. The seropositivity rate is defined as the percentage of seropositive subjects.

The mean geometric increase (MGI) of anti-gE antibody concentrations over pre-vaccination in the initial ZOSTER-041 study is defined as the geometric mean of the within subject ratios of the post-vaccination reciprocal anti-gE concentration to the Day 0 reciprocal anti-gE concentration.

The MGI of anti-gE antibody concentrations after revaccination over pre-revaccination is defined as the geometric mean of the within-subject ratios of the post-revaccination reciprocal anti-gE concentration to the Month 24 reciprocal anti-gE concentration.

4.2.2. Main analytical approach

4.2.2.1. Long-term follow-up phase

For persistence of humoral immunity measured after the primary vaccination course, the following parameters will be tabulated. ZOSTER-073 Day 1, study Month 12 and study Month 24 measurements will be displayed in tables and figures in terms of time since primary series in ZOSTER-041, grouped into 1 year intervals.

- GMCs of anti-gE antibody, MGI of post-vaccination timepoint over ZOSTER-041 pre-vaccination timepoint, and anti-gE antibody seropositivity rates with 95% CI;
  - GMCs of anti-gE antibody, MGI of post-vaccination timepoint over ZOSTER-041 pre-vaccination timepoint, and anti-gE antibody seropositivity rates with 95% CI will also be presented with Visit 1, Visit 2, and Visit 3 in the LTFU phase of ZOSTER-073 presented as Day 1, Month 12, and Month 24, in accordance to the primary endpoint timepoints.

- Descriptive statistics on anti-gE antibody concentrations (mean, SD, min, Q1, median, Q3, max);
- Vaccine response rates and 95% CIs to ZOSTER-041 pre-primary vaccination for anti-gE antibody concentrations;
- Descriptive statistics of the fold increase of post-vaccination timepoint over ZOSTER-041 pre-vaccination timepoint at ZOSTER-073 Day 1, study Month 12, and study Month 24 (mean, SD, min, Q1, median, Q3, max);
- Distribution of the fold over ZOSTER-041 pre-vaccination timepoint;
- The distribution of antibody titers will be tabulated and also presented using reverse cumulative curves.

Displays of GMCs of anti-gE antibody concentrations will also include all of the ZOSTER-041 timepoints.

Anti-gE antibody concentrations will be displayed graphically by time since primary vaccination dose 2. Values taken pre-primary vaccination, at 1 month post primary vaccination dose-1, and timepoints post-dose 2 of primary vaccination will be presented in separate symbols and colors in the figure, along with a trend line through post-dose 2 points. A line representing the median pre-vaccination concentration will be displayed for comparison.

4.2.2.2. Revaccination active phase

For humoral immunity after revaccination for the active phase, the following parameters will be tabulated. ZOSTER-073 study Months 24, 25, and 26 (Visits 3-5), will be presented as pre-revaccination, 1 month post-revaccination Dose 1, and 1 month post-revaccination Dose 2 in displays.

- GMCs of anti-gE antibody and anti-gE antibody seropositivity rates with 95% CI at pre-revaccination, 1 month post-revaccination Dose 1, and 1 month post-revaccination Dose 2;
- Vaccine response rates for anti-gE antibody concentrations at 1 month post-revaccination Dose 1 and 1 month post-revaccination Dose 2 [post- revaccination timepoint over pre-revaccination timepoint] with 95% CI;
- Vaccine response rates to ZOSTER-041 pre-primary vaccination for anti-gE antibody concentrations at 1 month post-revaccination Dose 1 and 1 month post-revaccination Dose 2 with 95% CI;
- MGI post-revaccination timepoint over pre-revaccination timepoint at 1 month post-revaccination Dose 1 and 1 month post-revaccination Dose 2 with 95% CI;
- MGI post-revaccination timepoint over ZOSTER-041 pre-vaccination timepoint at pre-revaccination, 1 month post-revaccination Dose 1, and 1 month post-revaccination Dose 2 with 95% CI;
- Descriptive statistics of the fold increase of anti-gE antibody concentrations 1 month post-revaccination Dose 1 and 1 month post-revaccination Dose 2 over pre-revaccination timepoint (mean, SD, min, Q1, median, Q3, max).

- Distribution of antibody titers at pre-revaccination, 1 month post-revaccination Dose 1, and 1 month post-revaccination Dose 2 will be tabulated and also presented using reverse cumulative curves.
- Boxplots of anti-gE antibody concentrations will be displayed by visit.

4.3. Secondary Endpoints Analyses

4.3.1. Secondary immunogenicity endpoints

The secondary immunogenicity analyses will use the same analysis sets as described in Section 4.2.

4.3.1.1. Definition of endpoints

Refer to Section 4.2.1.

4.3.1.2. Main analytical approach

4.3.1.2.1. Long-term follow-up phase

For persistence of cellular immunity after the primary vaccination course as determined by ICS, the following parameters will be tabulated. ZOSTER-073 Day 1, study Month 12 and study Month 24 measurements will be displayed in tables and figures in terms of time since primary series in ZOSTER-041, grouped into 1 year intervals.

- Descriptive statistics (N, mean, SD, min, Q1, median, Q3, max):
  - the frequency of gE specific CD4+T-cells secreting at least 2 activation markers (among IFN-γ, IL-2, TNF-α, CD40L);
  - the fold increase over ZOSTER-041 pre-vaccination timepoint for the frequency of gE-specific CD4(2+) T-cells;
- Vaccine response rates to ZOSTER-041 primary vaccination for frequency of gE-specific CD4(2+) T-cells will be tabulated with 95% CI.

CD4+T-cells secreting at least 2 activation markers will be displayed graphically by time since primary vaccination dose 2. Values taken pre-primary vaccination and post-dose 2 of primary vaccination will be presented in separate symbols and colors in the figure, along with a trend line through post-dose 2 points. A line representing the median pre-vaccination concentration will be displayed for comparison.

4.3.1.2.2. Revaccination active phase

For cellular immunity after revaccination as determined by ICS for the active phase, the following parameters will be tabulated. ZOSTER-073 study Months 24, 25 and 26 (Visits 3-5), will be presented as pre-revaccination, 1 month post-revaccination Dose 1, and 1 month post-revaccination Dose 2 in displays.

- Descriptive statistics (N, mean, SD, min, Q1, median, Q3, max):
  - the frequency of gE specific CD4+T-cells secreting at least 2 activation markers (among IFN-γ, IL-2, TNF-α, CD40L) at pre-revaccination, 1 month post-revaccination Dose 1, and 1 month post-revaccination Dose 2;
  - the fold increase over pre-revaccination timepoint Month 24 in the frequency of gE specific CD4[2+] T-cells at 1 month post-revaccination Dose 1 and 1 month post-revaccination Dose 2.
  - the fold increase over ZOSTER-041 pre-vaccination timepoint in the frequency of gE specific CD4[2+] T-cells at pre-revaccination, 1 month post-revaccination Dose 1, and 1 month post-revaccination Dose 2.
- Vaccine response rates for frequency of gE-specific CD4(2+) T-cells at 1 month post-revaccination Dose 1 and 1 month post-revaccination Dose 2 over pre-revaccination timepoint Month 24 will be tabulated with 95% CI.
- Vaccine response rates to ZOSTER-041 primary vaccination for frequency of gE-specific CD4(2+) T-cells at pre-revaccination, 1 month post-revaccination Dose 1, and 1 month post-revaccination Dose 2 will be tabulated with 95% CI.

CD4+T-cells secreting at least 2 activation markers will also be displayed graphically by timepoint.

4.3.1.2.3. Revaccination follow-up phase

For **humoral immunity** after revaccination (revaccination follow-up phase), the following parameters will be tabulated. ZOSTER-073 study Months 37 and 49 (Visit 6 and Visit 7) data will be presented in terms of time since revaccination, grouped in appropriate month intervals, based on the distribution subjects' visit occurrence. For non-revaccinated subjects, separate summaries will be provided, and data will be presented on time since primary vaccination in ZOSTER-041.

- GMC of anti-gE antibody and anti-gE seropositivity rates with 95%;
- Vaccine response rates for anti-gE antibody concentrations over pre-revaccination timepoint with 95% CI;
- Vaccine response rates to ZOSTER-041 pre-primary vaccination for anti-gE antibody concentrations with 95% CI;
- MGI post-revaccination over pre-revaccination timepoint with 95% CI;
- MGI post-revaccination over ZOSTER-041 pre-vaccination timepoint with 95% CI
- MGI post-revaccination dose 1 over 1 month post primary vaccination dose 2 with 95% CI
- Descriptive statistics of the fold increase of anti-gE antibody concentrations over pre-revaccination timepoint (mean, standard deviation, min, Q1, median, Q3, max).

- Descriptive statistics of the fold increase of anti-gE antibody concentrations over ZOSTER-041 pre-vaccination timepoint (mean, SD, min, Q1, median, Q3, max).
- Distribution of antibody titers will be tabulated and also presented using reverse cumulative curves.
- Boxplots of anti-gE antibody concentrations will be displayed by visit.

For **cellular immunity** after revaccination (revaccination follow-up phase) as determined by ICS, the following parameters will be tabulated. ZOSTER-073 study Months 37 and 49 (Visit 6 and Visit 7) data will be presented in terms of time since revaccination, grouped in appropriate month intervals, based on the distribution subjects' visit occurrence. For non-revaccinated subjects, separate summaries will be provided, and data will be presented on time since primary vaccination in ZOSTER-041.

- Descriptive statistics (N, mean, SD, min, Q1, median, Q3, max):
  - the frequency of gE specific CD4+T-cells secreting at least 2 activation markers (among IFN-γ, IL-2, TNF-α, CD40L);
  - the fold increase over pre-revaccination timepoint in the frequency of gE specific CD4[2+] T-cells.
- Vaccine response rates for frequency of gE-specific CD4(2+) T-cells over pre-revaccination timepoint will be tabulated with 95% CI. Vaccine response rate is defined in Section 6.2.6.4.

4.3.2. Secondary safety endpoints

Safety analyses will be performed on the Enrolled Set for the LTFU phase and the ES for the revaccination phase. All analyses of solicited and unsolicited AEs will be performed overall and by age stratum (based on age at the time of primary vaccination in ZOSTER-041 for the LTFU phase, based on age at the time of revaccination in ZOSTER-073 for revaccination active and follow-up phases).

If the number of subjects with the particular AE is too small (less than [10%] of the sample size), the safety table may not be provided by age stratum.

For solicited AE summaries, the denominators used for deriving percentages will include all revaccinated subjects with at least one solicited local or solicited general symptom documented as either present or absent.

4.3.2.1. Long-term follow-up phase

The results for the analysis of safety in the long-term follow-up phase will be tabulated as follows:

- Number and percentage of subjects reporting at least one SAE related to primary vaccination in study ZOSTER-041 classified by Medical Dictionary for Regulatory Activities (MedDRA) Primary System Organ Class (SOC) and Preferred Term (PT) from the day after

ZOSTER-041 last study visit (Month 13) to ZOSTER-073 pre-revaccination (Visit 3 Month 24) will be tabulated with exact 95% CI.

- Number and percentage of subjects with at least one suspected or biopsy-proven allograft rejection from ZOSTER-041 last visit (Month 13) to ZOSTER-073 Day 1 will be tabulated with exact 95% CI.
- Number and percentage of subjects with at least one biopsy-proven allograft rejection from ZOSTER-073 Day 1 to ZOSTER-073 pre-revaccination (Visit 3 Month 24) will be tabulated with exact 95% CI.
- Number and percentage of subjects with suspected or confirmed HZ cases from ZOSTER-041 last visit (Month 13) to study ZOSTER-073 Day 1 will be tabulated with exact 95% CI.
- Number and percentage of subjects with confirmed HZ cases from ZOSTER-073 Day 1 through ZOSTER-073 study Month 24 will be tabulated with exact 95% CI.
- Listing of subjects with history of suspected allograft rejection or history of biopsy-proven allograft rejections from ZOSTER-041 last study visit to ZOSTER-073 Day 1 will be provided.
- Listing of subjects with biopsy-proven allograft rejections from ZOSTER-073 Day 1 onward will be provided.
- Listing of subjects with a suspected or confirmed HZ episode from ZOSTER-041 last study visit to ZOSTER-073 Day 1 will be provided.
- Listing of subjects with a confirmed HZ episode from ZOSTER-073 Day 1 onward will be provided.
- Number of subjects with declining allograft function (following HZ and allograft rejection episodes), as determined by fold change from baseline serum creatinine measurements, for the time period from study ZOSTER-041 last visit (Month 13) to study ZOSTER-073 Visit 3 (Month 24). This serum creatinine fold change from baseline will be summarized descriptively. A list of subjects with an increase in serum creatinine will also be presented. Allograft dysfunction is defined as having a fold increase in serum creatinine of 1.2 or greater from the reference timepoint.

4.3.2.2. Revaccination phase

The results for the analysis of safety in the revaccination phase will be tabulated as follows:

- Number and percentage of subjects with at least one local AE (solicited and unsolicited), with at least one general AE (solicited and unsolicited), and with any AEs during the solicited 7-day follow-up period will be tabulated with exact 95% CI after each revaccination dose and overall. The same computations will be done for Grade 3 AEs and medically attended AEs. Number and percentage of subjects reporting each individual solicited local AE (any grade and Grade 3) and solicited general AE (any grade, Grade 3, any related and Grade 3 related) during the 7-day follow-up period (i.e., on the day of

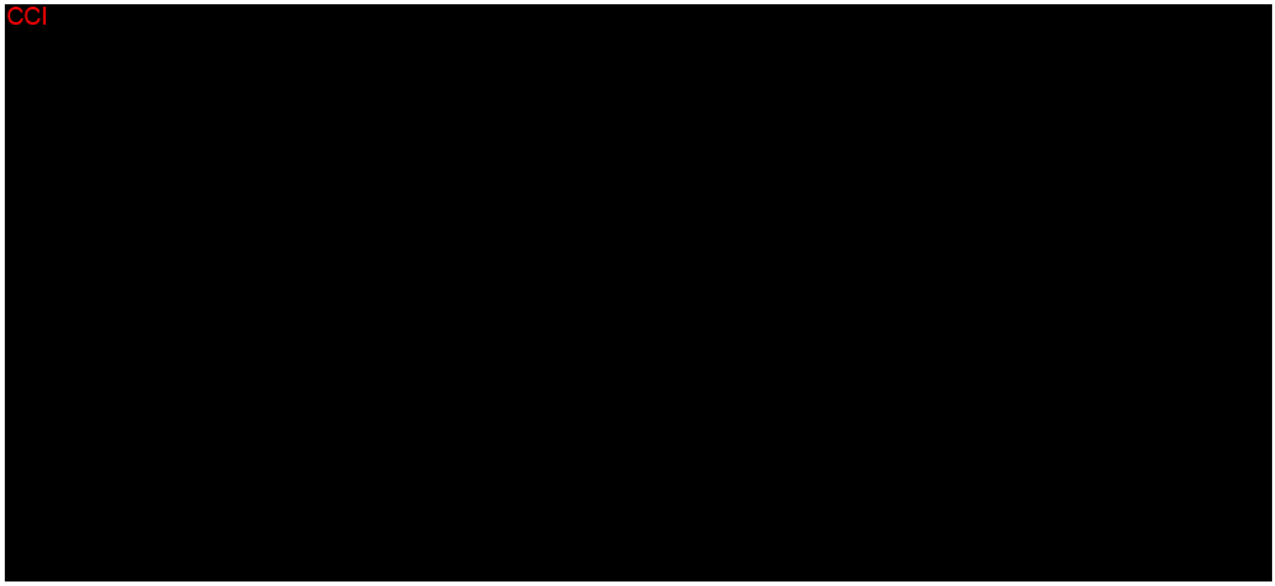
revaccination and 6 subsequent days) will be tabulated after each revaccination dose and overall.

- Duration of solicited local and solicited general AEs within 7 days and entire duration (lasting longer than 7 days) will be tabulated descriptively overall.
- Number and percentage of subjects with any unsolicited AEs during the 30-day follow-up period (i.e., on the day of revaccination and 29 subsequent days) with its exact 95% CI will be tabulated by MedDRA Primary SOC and PT. Similar tabulations will be done for Grade 3 unsolicited AEs, for any causally related unsolicited AEs, for Grade 3 causally related unsolicited AEs, for Grade 3 non-serious unsolicited AEs, for Grade 3 causally related non-serious unsolicited AEs, non-serious unsolicited AEs, non-serious causally related unsolicited AEs, and for unsolicited AEs resulting in a medically attended visit.
    - The number and percentage doses followed by unsolicited AEs during the 30-day follow-up period with its exact 95% CI will also be tabulated.
- Number and percentage of subjects with at least one report of SAE classified by MedDRA Primary SOC and PT and reported from revaccination Dose 1 up to 30 days post-last revaccination dose,from revaccination Dose 1 up to 12 months post- last revaccination dose, and from revaccination Dose 1 up to study end will be tabulated with exact 95% CI.
- Number and percentage of subjects with at least one report of causally related-SAE classified by MedDRA Primary SOC and PT and reported from revaccination Dose 1 up to 30 days post-last revaccination dose,from revaccination Dose 1 up to 12 months post-last revaccination dose, and from revaccination Dose 1 up to study end will be tabulated with exact 95% CI.
- Number and percentage of subjects with at least one pIMD classified by MedDRA Primary SOC and PT and percentage of subjects with at least one pIMD with causal relationship, reported from revaccination Dose 1 up to 30 days,from revaccination Dose 1 up to 12 months post-last revaccination dose, and from revaccination Dose 1 up to study end will be tabulated with exact 95% CI.
- Number and percentage of subjects with at least one biopsy-proven allograft rejection and biopsy-proven allograft rejection with causal relationship reported from revaccination Dose 1 up to study end will be tabulated with exact 95% CI.
- Number and percentage of subjects with at least one biopsy-proven allograft rejection and biopsy-proven allograft rejection with causal relationship reported from revaccination Dose 1 up to 12 months post last revaccination will be tabulated with exact 95% CI.
- Number and percentage of subjects with fatal SAEs and causally related fatal SAEs classified by MedDRA Primary SOC and PT will be presented. Fatal SAEs and related fatal SAEs will also be described by onset date of SAE and date of death as follows:
    - With onset date of fatal SAE during the period starting from revaccination Dose 1 to 30 days post last revaccination dose, from revaccination Dose 1 up to 12 months post last revaccination, and from revaccination Dose 1 up to study end

  - Who died (date of death) during the period starting from revaccination Dose 1 up to 30 days post last revaccination dose, from revaccination Dose 1 up to 12 months post last revaccination, and from first revaccination to study end.

- SAEs and pIMDs will be listed. These listings will include all fields on the CRF, including but not limited to, verbatim event description, MedDRA SOC/PT, start/stop study days, site, intensity (maximum and at time of onset), relationship to study vaccine, outcome.
- Listing of withdrawals due to AE and SAEs will be provided, including verbatim event description, MedDRA SOC/PT, start/stop study days, site, intensity (maximum and at time of onset), relationship to study vaccine, outcome
- Listing of subjects with confirmed HZ episode from Dose 1 of revaccination (Month 24) up to study end will be provided.
- Listing of subjects with biopsy-proven allograft rejection from Dose 1 of revaccination (study Month 24) up to study end will be provided. For subjects with an episode of biopsy-proven rejection, dates of biopsy-proven rejection episodes, treatment given (including dialysis), intensity, and rejection outcome will be included in the listing of renal transplant rejection history.
- Number and percentage of subjects with declining allograft function (following revaccination, HZ episode, and allograft rejection), as determined by serum creatinine measurements. Serum creatinine values will be summarized descriptively. See Section 4.5.3.1 for more details. Allograft dysfunction is defined as having a fold increase in serum creatinine of 1.2 or greater from the reference timepoint.

The listings will contain all events (HZ episodes, rejections) and columns will be included to indicate timing (up to Day 1, Before revaccination, et.)



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4.5. Other Safety Analyses

Safety analyses will be performed on the Enrolled Set for the LTFU phase. For the revaccinated subjects the Exposed Set for revaccination phase will be used. For non-revaccinated subjects, the Enrolled Set will be used to compare to revaccinated subjects past ZOSTER-073 Visit 3.

4.5.1. Extent of Exposure

The number of subjects receiving each revaccination dose will be tabulated as part as subject disposition and compliance. See Section 6.1.1 and Section 6.1.5 for more details.

4.5.2. Adverse Events

Adverse event analyses are described in Section 4.3.2.

Adverse events will be coded using the standard Medical Dictionary for Regulatory Activities (MedDRA) and graded by the investigator. Intensity scales for solicited local and solicited general events can be found in protocol section 12.5.9.1.2.

4.5.2.1. Adverse Events of Special Interest

For this trial, AESIs will be defined as:

- potential immune-mediated diseases
- renal allograft rejection (biopsy proven)

Analyses of these events are described in Section 4.3.2.

4.5.2.2. COVID-19 Assessment

The number of subjects with suspected, probable, or confirmed COVID-19 infection will be presented along with number of subjects with positive, negative, or indeterminate diagnosis test results.

A standardized MedDRA Query (SMQ) will be used to identify all AEs related to COVID-19.The overall incidence of AEs and SAEs of COVID-19 and COVID-19 AEs leading to study intervention discontinuation or study withdrawal will be summarized.

4.5.2.3. Impact of COVID-19 Pandemic on Safety Results

Pandemic measures began in different countries at different times. A dataset containing the date when pandemic measures began, as determined by the GSK country Issue Management Teams (IMT), will be used to determine the start date of each wave of pandemic measures within each country.

4.5.3. Additional Safety Assessments

4.5.3.1. Laboratory Data

Allograft dysfunction will be assessed through serum creatinine measurements. The number and percentage with an increase from baseline (≥1.2, ≥1.5, ≥1.75, ≥2 fold) in serum creatinine related to allograft rejection episodes, revaccination, and HZ episodes. will be tabulated based on whether the episode fell in the time frames outlined in Section 4.3.2.1 and Section 4.3.2.2

See Section 6.2.3 for definitions of baseline and handling post-baseline measurements related to rejection episodes, revaccination, and HZ episodes.

A listing of raw serum creatinine measurements and their corresponding fold increase from baseline will be provided for each individual subject. Changes from baseline and percent changes from baseline will also be included for each subject, along with their primary and revaccination dates, if applicable.

Replacement kidney since ZOSTER-041 will also be listed.

4.5.3.2. Vital Signs

Weight recorded at each ZOSTER-073 study visit and change from baseline for each individual will be presented in a listing. See Section 4.1.2 for definitions of baseline for each study phase.

4.5.3.3. Zoster Brief Pain Inventory

A listing of subjects reporting pain caused by shingles in the last 24 hours on the Zoster Brief Pain Inventory (ZBPI) will be provided. Pain ratings and along with the areas of pain will be included in the listing.

4.5.3.4. HZ Episodes

Suspected episodes of HZ will be identified via the HZ episode status eCRF.

Confirmed episodes of HZ will be identified via Polymerase Chain Reaction (PCR) test on HZ lesion sample.

The number of subjects with HZ episodes will be tabulated as follows:

- From ZOSTER-041 last visit (Month 13) to ZOSTER-073 Day 1
- From ZOSTER-073 Day 1 through ZOSTER-073 study Month 24
- From first revaccination up to study end

The number and percentage of non-revaccinated subjects reporting the occurrence of HZ episodes from visit 3 (Month 24) up to study end will also be presented.

All suspected and confirmed HZ episodes occurring between the end of ZOSTER-41 and ZOSTER-073 enrollment and occurring after ZOSTER-073 will be listed.

Immunosuppressive therapies before, during, and after the episode will be listed for subjects with HZ episodes in the concomitant medications listing.

GMCs of anti-gE antibody and CD4+T-cells secreting at least 2 activation markers in subjects who had suspected and/or confirmed HZ episodes will be displayed graphically. Values taken before and after the episode will be indicated using different colors and symbols in the figure.

4.6. Other Analyses

4.6.1. Subgroup analyses

The primary immunogenicity endpoints will not be presented by subgroup. Subgroup analyses of the secondary safety endpoints will be performed by age group only. If the number of subjects with the particular AE is too small (less than [10%] of the sample size), the safety table may not be provided by age stratum.

If the number of subjects is too small (less than [10%]) within a subgroup, then the subgroup categories may be redefined prior to locking the study. See Table 2 for the subgroup category definitions and presentations.

Sub-groups (endpoint)	Order in tables	Label in tables	Definition for footnote
Age strata (Safety endpoints)	1	18-49ys	Subjects aged between 18 and 49 years
	2	>= 50ys	Subjects aged 50 years and older
Combination of types of maintenance immuno-suppressive therapy in use (demography)*[$]	1	All 3 classes: CIS + CS + MC	Subjects using calcineurin inhibitor or sirolimus, corticosteroids and mycophenolate compound as maintenance immunosuppressive therapy at Visit X
	2	Any 2 class combinations of CIS, CS, or MC	Subjects using any combination of any two of three classes of immunosuppressant: 1) Calcineurin or mTOR inhibitors such as cyclosporine, sirolimus, or tacrolimus, everolimus; 2) Corticosteroids such as prednisone; and 3) Mycophenolate compounds as maintenance immunosuppressive therapy at Visit X
	3	Any single class: CIS, CS, or MC	Subjects using any single class of immunosuppressant: 1) Calcineurin or mTOR inhibitors such as cyclosporine, sirolimus, or tacrolimus, everolimus; 2) Corticosteroids such as prednisone; and 3) Mycophenolate compounds as maintenance immunosuppressive therapy at Visit X

* The combination of types of immunosuppressive therapy that are not applicable will not be displayed in the statistical tables. [$]Visit X will be replaced with the primary vaccination visit, or first revaccination visit as applicable, per phase.

4.6.2. Sensitivity Analyses

4.6.2.1. Dialysis Recipients

Subjects who receive dialysis after revaccination will be excluded from the primary and secondary analyses as part of the elimination criteria defined in Section 3.1. Summaries of GMCs of anti-gE antibody, anti-gE antibody seropositivity rates with 95% CI, and frequency of

gE specific CD4+T-cells secreting at least 2 activation markers (among IFN-γ, IL-2, TNF-α, CD40L) will be provided separately for dialysis recipients for the revaccination follow-up phase. An additional sensitivity analysis may be performed in which these subjects' results are included with the rest of the PPS for persistence after revaccination course (revaccination follow-up phase).

4.7. Interim Analyses

Limited long-term immunogenicity analyses were performed from ZOSTER-041 Visit 3 (Month 2) to ZOSTER-073 Visit 1 (Day 1) and from ZOSTER-041 Visit 3 (Month 2) to ZOSTER-073 Visit 2 (study Month 12). These intermediate analyses are described in separate project data analysis plans.

A descriptive interim analysis after the revaccination active phase is planned and will be performed one month after the second revaccination dose, study Month 26 (Visit 5). No CSR will be written during the interim analysis. The following will be assessed:

- Long-term safety from ZOSTER-041 Visit 5 (Month 13) to ZOSTER-073 Visit 3 (study Month 24).
- Persistence of immunogenicity from ZOSTER-041 Visit 3 (Month 2) to ZOSTER-073 Visit 3 (study Month 24).
- Safety and immunogenicity after revaccination from ZOSTER-073 Visit 3 (Month 24) to ZOSTER-073 Visit 5 (study Month 26).

The interim analysis will include:

- Primary and secondary immunogenicity endpoints for the LTFU phase and revaccination active phase;
- Secondary safety endpoints for the LTFU phase;
- Reactogenicity data after each administered revaccination dose;
- Unsolicited AEs (serious and non-serious) will also be included up to 30 days follow-up post each revaccination dose;
- SAEs, AESIs (pIMDs and biopsy-proven allograft rejections), withdrawals due to AE and SAEs, confirmed HZ episodes, allograft dysfunctions (following revaccination, HZ episode, and allograft rejection), serum creatinine measurements until the Data Lock Point (DLP).

A final analysis on immunogenicity and safety will be performed at study end (Visit 7) once all data are available and cleaned.

The final study report will contain at least the final analyses of all primary and secondary endpoints. CCI [redacted]

4.8. Changes to Protocol Defined Analyses

The protocol states the Enrolled Set will be used for analyses of safety and immunogenicity for non-revaccinated subjects, however, the PPS for analysis of persistence (LTFU phase) was amended in this SAP such that it includes Visit 6 (study Month 37) and Visit 7 (study Month 49) for non-revaccinated subjects, therefore, the PPS for analysis of persistence will be used for analyses of immunogenicity and the Enrolled Set will be used for analyses of safety in non-revaccinated subjects.

The protocol states the percentage of subjects reporting at least one SAE related to primary vaccination classified by MedDRA Primary SOC and PT from ZOSTER-041 Day 1 to ZOSTER-073 pre-revaccination will be tabulated with exact 95% CI. Any SAEs related to primary vaccination from ZOSTER-041 Day 1 through the last ZOSTER-041 study visit will be taken from the ZOSTER-041 CSR. Any SAEs that occurred after the last ZOSTER-041 study visit and through ZOSTER-073 pre-revaccination will be captured on the ZOSTER-073 CRFs and summarized according to Section 4.3.2.1.

5. SAMPLE SIZE DETERMINATION

ZOSTER-041 subjects, who had a complete vaccination course (2 doses of HZ/su vaccine) will be offered enrollment into study ZOSTER-073 at participating centers.

Up to a maximum of 86 subjects meeting the eligibility criteria for enrollment (2 doses of HZ/su vaccine in ZOSTER-041) will be targeted for enrollment in participating centers. Approximately 15% of the enrolled subjects might withdraw or not be evaluable for immunogenicity, therefore the target sample size will be approximately 73 subjects evaluable for humoral immunogenicity in the per protocol sets defined in Section 3.

Up to a maximum of 40 subjects will be targeted for the Cell-Mediated Immunity (CMI) sub-cohort in participating centers having CMI capabilities in order to reach 33 evaluable subjects for CMI analyses, assuming a 15% of drop-out and non-evaluability rate. CMI subjects from ZOSTER-041 will be enrolled into the ZOSTER-073 CMI sub-cohort. Also, the balance of CMI subjects to be enrolled will be selected at random from CMI participating centers (having CMI capabilities) to complete the sub-cohort up to 40 subjects at ZOSTER-073 Visit 1 (Day 1).

Subjects who prematurely withdrew from study will not be replaced.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 Study Population Analyses

6.1.1. Subject Disposition

The number of subjects enrolled into the study as well as the number of subjects excluded from each analysis set will be presented through a CONSORT table showing the subject disposition

from the Enrolled Set to each PPS as well as the ES. Enrollment by country will be presented as part of demographic summaries.

A summary of the number and percentage of subjects who completed the study as well as those who prematurely withdrew from the study will be provided. Reasons for study withdrawal will be summarized. For those who have neither completed nor withdrawn, they will be categorized as in follow-up. This analysis will be based on the Enrolled Set.

A summary of study intervention status will be provided. This display will show the number and percentage of subjects who have completed each dose of the scheduled study vaccine, are ongoing with study intervention, or have discontinued study intervention prematurely, as well as primary reasons for discontinuation of study intervention. This analysis will be based on the ES.

6.1.2. Demographic and Baseline Characteristics

The demographic characteristics including age (in years at the time of primary vaccination in ZOSTER-041, in years at the time of enrollment in ZOSTER-073, and in years at first revaccination in ZOSTER-073), gender, ethnicity, baseline weight and race will be summarized with descriptive statistics. In addition, the following age categories will be summarized: 18-49, and >=50 YOA (according to subgroups), as well as 18-64, 65-84 and >=85 YOA (needed for publishing) based on the Enrolled Set. Age will be calculated as the number of years between the date of birth and the date of primary vaccination/enrollment/re-vaccination. Missing demographic variables will not be replaced.

Demographic summaries will be provided overall, by age at the time of primary vaccination in ZOSTER-041, and by maintenance immunosuppressive therapy at the time of primary vaccination in ZOSTER-041.

Medical history since the last study ZOSTER-041 visit will be listed. Uncoded medical history will be summarized under ‘Other’ category. Medical history for subjects with confirmed, probable, and suspected diagnosis of COVID-19 AEs can be obtained from the medical history listing.

Renal transplant rejection history and replacement kidney will also be listed for the Enrolled Set. Smoking history will be part of the medical history listing.

6.1.3. Protocol Deviations

Important protocol deviations including those related to COVID-19 will be summarized and listed. Protocol deviations which result in exclusion from an analysis set will also be summarized. Data will be reviewed prior to freezing and locking the database to ensure all deviations leading to analysis population exclusions are captured and categorised in the protocol deviations ADaM dataset.

There are also situations that are not deviations, but would require an elimination, e.g. a participant may elect or not be eligible to be revaccinated, and are excluded from revaccinated

set but included in long-term follow-up from primary vaccination series. These will be summarized with the protocol deviations resulting in exclusion.

6.1.4. Prior and Concomitant Medications and Vaccinations

The number and percentage of subjects with concomitant medications (including the following immunosuppressive therapy categories: maintenance, therapeutic, and chronic use and well as anti-viral treatment for HZ, pain rescue medication to control HZ pain, and other therapy for HZ as well as pain rescue medication to control HZ pain and other therapy for HZ) will be summarized during the 30-day follow-up period after each vaccine administration and overall. While maintenance and therapeutic immunosuppressive therapies are used for prevention of transplant rejection, a chronic use immunosuppressive therapy is for a difference purpose yet may have still an impact on immune response so will also be tabulated.

Concomitant vaccinations and concomitant immunosuppressive medications will be listed. Concomitant medications and vaccinations will be coded using both the GSK Drug and WHO Drug dictionaries. Anatomical Therapeutic Chemical (ATC) classifications will appear in the listing. Duration of therapeutic immunosuppressive therapy will be displayed in the listing of concomitant medications.

Concomitant COVID-19 vaccination before and during the study will be presented with concomitant vaccination/vaccination history listings.

6.1.5. Study Intervention Compliance

The number of doses administered will be tabulated as will the percentage of subjects who have completed each dose of the scheduled study vaccine.

The number and percentage of subjects who returned the dairy cards and those who returned the dairy cards with documentation of the presence or absence of AEs will be tabulated for the ES. Compliance in completing solicited AEs information will be tabulated after each dose and overall.

Summaries of the time intervals between study visits will be tabulated based on the Enrolled Set.

6.1.6. Additional Analyses Due to the COVID-19 Pandemic

Depending on how the COVID-19 pandemic evolves, the SAP may be amended to reflect the additional analyses corresponding to COVID-19.

6.2. Appendix 2 Data Derivations Rule

This section contains standard rules for data display and derivation for clinical and studies.

6.2.1. Baseline Immunogenicity

For the LTFU phase, baseline is latest non-missing pre-primary series dose assessment from ZOSTER-041 study. For non-revaccinated subjects, at ZOSTER-073 Visit 6 and Visit 7, baseline is also latest non-missing pre-primary series dose assessment from ZOSTER-041 study.

For the revaccination active and follow-up phases, baseline is the latest pre-revaccination dose assessment with a non-missing result from ZOSTER-073.

6.2.2. Assessment Window

For data summaries by visit, scheduled visits with nominal visit description will be displayed. Unscheduled visits will not be displayed or allocated into a visit window. All unscheduled visits will be displayed in the listing.

6.2.3. Multiple measurements at One Analysis Time Point

Baseline and post-baseline serum creatinine measures are computed as follows:

- For Allograft rejection:
    - The average of measurements 2 months prior to a biopsy-proven allograft rejection will be used as event baseline. If there are not 2 or more measurements in 2 months, then go back to 3 or 4 months prior to biopsy to have a minimum of 2 measurements.
    - The maximum of measurements taken up to 2 months after resolution of the biopsy-proven rejection, so that 2 or more additional post-rejection measurements are recorded, will be used to determine declining allograft function compared to baseline pre-allograft rejection measurements.

- For revaccination:
    - The average of measurements taken 3 months prior to first revaccination, Visit 3 (Month 24), will be used as pre-vaccination baseline. If there are not 3 or more measurements in 3 months, then go back to 4 or 5 months prior to revaccination to have a minimum of 3 measurements.
    - The maximum of measurements taken up to 3 months after last revaccination, Visit 5 (Month 26), so that 3 or more additional post-revaccination measurements are recorded, will be used to determine declining allograft function compared to pre-revaccination

- For episode of HZ cases:
    - The average of measurements taken 2 months prior to a HZ episode, will be used as event baseline. If there are not 2 or more measurements in 2 months, then go back to 3 or 4 months prior to HZ episode to have a minimum of 2 measurements.
    - The maximum of measurements taken up to 2 months after HZ episode rash resolution, so that 2 or more post-HZ resolution measurements are recorded, will be used to determine declining allograft function compared to pre-HZ episode.

- For non-revaccinated subjects:

- The mean of the available values before primary vaccination is used as baseline value.
- The maximum of the available values after Visit 3 Month 24 up to study end is used for calculating fold increase

As described in Section 1.2, since the interval between the end of ZOSTER-041 study and the start of this ZOSTER-073 study will vary per subject, yearly timeframes will be defined around the anniversary date post vaccination for the first ZOSTER-073 blood sample and incremented by 1 year each visit after. As such, the same interval may include one subject's data from ZOSTER-073 Visit 1 and another subject's Visit 2 data due to overlapping in timepoints by study year associated with the long-term follow-up phase.

6.2.4. Attributing events to vaccine doses

The dose relative to an event is the most recent vaccine dose given to a subject prior to the start of a given event. For example, if the start date of an adverse event is between Dose 1 and Dose 2, the relative dose will be Dose 1.

If an event starts on the same day as a study dose, the relative dose will be derived from the additional information provided in the case report form (CRF) using the contents of the flag indicating if the event occurred before or after study dose. If 'after vaccination ' is selected, the relative dose for the event will be the one administered on the start day of the event. If 'vaccination' is selected, the relative dose for the event will be the dose prior to this one.

The number of doses is the number of times the vaccine was administered to a subject

6.2.5. Handling of Missing Data

6.2.5.1. Dates

When partially completed dates (i.e., dates missing a day and/or month) are used in calculations, the following standard rules will be applied:

- A missing day will be replaced by 15
- A missing day and month will be replaced by June 30th.

The following exceptions apply:

When partially completed dates (i.e., with missing day or month) are used in calculations, the following rules will be applied:

- Adverse event start dates with missing day:
  - If the month is not the same as the vaccine dose, then the imputed start date will be the 1st of the month
  - If the event starts in the same month as at least one of the study vaccines, the flag indicating if the event occurred before or after study vaccine (AE.AESTRTPT) will be

used to complete the date. If 'after vaccination' is selected, the imputed start date will match the study vaccine dose given during that month. If 'before vaccination' is selected, the imputed date will be one day before the study vaccine dose given during that month.

- Adverse event start dates with missing day and month:
  - If the year is not the same as the vaccine dose, then the imputed start date will be the 1st of January.
  - If the event starts in the same year as the vaccine dose, the flag indicating if the event occurred before or after vaccination (AE.AESTRTPT) will be used to complete the date. If 'after vaccination' is selected, the imputed start date will match the first study vaccine dose given during that year. If 'before vaccination' is selected, the imputed date will be one day before the first study vaccine dose given during that year.
- Adverse event end dates with missing day: the imputed end date will be the last day of the month (30 or 31) or the study conclusion date whichever comes first.
- Adverse event end dates with missing day and month: the imputed end date will be the last day of the year (31st of December) or the study conclusion date whichever comes first.

All incomplete medical history and concomitant medication/vaccination start/end dates will follow the rules above.

6.2.5.2. Laboratory Data

Missing laboratory results (immunological) will not be replaced.

6.2.5.3. Daily Recording of solicited events

For studies using paper diaries which have questions in the eCRF indicating the presence or absence of solicited events, the following rules are applicable:

- Denominators for the summary of administration site (or systemic) solicited events will be calculated using the number of subjects who respond "Yes" or "No" to the question concerning the occurrence of administration site (or systemic) events.
- When a specific solicited event is marked as having not occurred following a specific study dose (i.e., SDTM CE.CEOCCUR=N for the specified post-dose period for the event in question), all daily measurements will be imputed as Grade 0.
- When a specific solicited event is marked as having occurred following a specific study dose (i.e., SDTM CE.CEOCCUR=Y for the specified post-dose period for the event in question), any missing daily recordings will be given imputed values to allow them to contribute to the 'Any' rows but not to specific grade rows of the solicited event summary tables.
- When the occurrence of a specific solicited event is not present (i.e. SDTM CE.CEOCCUR is neither Y nor N for the specified post-dose period for the event in question) but the group

of solicited events (administration site or systemic) is marked as having occurred (i.e. SDTM CE.CEOCCUR=Y), all missing daily recordings will be given imputed values to allow them to contribute to the 'Any' rows but not to specific grade rows of the solicited event summary tables.

Note while fever is a solicited systemic event, it was not included in the group of solicited events in the eCRF question, therefore will only contribute to the 'Any' and specific grade rows if it occurred.

- The following table shows how subjects contribute to each category for a specific solicited event over the Day X to Day Y post-dose period:

Solicited event category	Subjects included in the calculation of the numerator
Any	All subjects with at least one occurrence of the adverse event at grade 1, grade 2, or grade 3 between Day X and Day Y or with the adverse event marked as present and at least one missing daily recording between Day X and Day Y
At least grade 1	All subjects with at least one occurrence of the adverse event at grade 1, grade 2, or grade 3 between Day X and Day Y
At least grade 2	All subjects with at least one occurrence of the adverse event at grade 2 or grade 3 between Day X and Day Y
At least grade 3	All subjects with at least one occurrence of the adverse event at grade 3 between Day X and Day Y

6.2.5.4. Unsolicited adverse events

Missing severity, relationship with study vaccine, and outcome of unsolicited AEs will not be replaced and will appear as 'UNKNOWN' when displayed in a statistical output.

Unsolicited AE summaries will include SAEs unless specified otherwise.

As per CDISC Vaccines Therapeutic Area guide, the solicited events which continue beyond the observation period are stored in the AE domain, but they do not contribute to the summaries of unsolicited AEs.

6.2.6. Data Derivations

6.2.6.1. Age

When age at primary vaccination in ZOSTER-041, at time of enrollment in ZOSTER-073, and at first revaccination in ZOSTER-073 is to be displayed in years, it will be calculated as the number of complete calendar years between the year of birth and the date of primary vaccination/enrollment/revaccination. For example:

DOB = 10SEP1983, Date of primary vaccination = 09SEP2018 -> Age = 34 years

DOB = 10SEP1983, Date of primary vaccination = 10SEP2018 -> Age = 35 years

In case of partial dates, the rules in Section 6.2.5.1 will be followed.

6.2.6.2. Vital signs

- Weight will be presented in kilograms. Weights reported in pounds will be converted as follows:
  Weight in kilograms = Weight in pounds / 2.2

The results will be rounded to 1 decimal digit.

- Temperature ranges for fever are as follows:
  - Grade 0: <38.0 C
  - Grade 1: ≥38.0 – ≤38.5
  - Grade 2: >38.5 – ≤39.0
  - Grade 3: >39.0

6.2.6.3. Numerical serology results

Numerical serology results will be derived from the content of IS.ISORRES in the SDTM dataset. For assays with a specific cut-off and a specific upper limit of quantification (ULOQ), the following derivation rules apply:

IS.ISORRES	Derived value
"NEG", "-", or "(-)"	cut-off/2
"POS", "+", or "(+)"	cut-off
"< value" and value is <= assay cut-off	cut-off/2
"< value" and value is > assay cut-off	value
"> value" and value is < assay cut-off	cut-off/2
"> value" and value is >= assay cut-off	value
"value" and value is < cut-off	cut-off/2
"value" and value is >= cut-off and value is <=ULOQ	value
"value" and value is > ULOQ	ULOQ
All other cases	missing

6.2.6.4. Cellular-mediated immune response

- For the descriptive analyses, the frequency of CD4 [2+] T-cells upon in vitro stimulation with the gE (induction condition) is calculated by dividing the number of activated CD4 [2+] T-cells (numerator) over the total number of CD4 T-cells involved (denominator).

$$Freq_{Induction}^{CD4[2+]} = \frac{n_{Induction}^{2+}}{N_{Induction}^{CD4}}$$

$n_{Induction}^{2+}$ = number of CD4 T cells secreting at least 2 activation markers after induction with the antigen

N^{CD4} = Total number of CD4 T cells involved in the assay (induction)

- The frequency of **gE-specific** CD4$^+$ T-cells (*Spec-CD4[2+])* for each individual subject is calculated as the difference between the frequency of CD4[2+], upon in vitro stimulation with the gE-antigen (induction condition) minus the frequency of (CD4[2+] upon in vitro stimulation in medium only (background condition). The differences less or equal to one (1) are imputed to 1 gE-specific activation marker expressing CD4[2+] T-cell per 10^6 CD4$^+$ T-cells.

$$Freq_{Specific}^{CD4[2+]} = \frac{n_{Induction}^{2+}}{N_{Induction}^{CD4}} - \frac{n_{Background}^{2+}}{N_{Background}^{CD4}} \qquad if \ \frac{n_{Induction}^{2+}}{N_{Induction}^{CD4}} > 1 + \frac{n_{Background}^{2+}}{N_{Background}^{CD4}}$$

$$Freq_{Specific}^{CD4[2+]} = 1 \qquad if \ \frac{n_{Induction}^{2+}}{N_{Induction}^{CD4}} \le 1 + \frac{n_{Background}^{2+}}{N_{Background}^{CD4}}$$

$n_{Induction}^{2+}$ = number of CD4 T-cells secreting at least 2 activation markers after induction with the gE-antigen

$n_{Background}^{2+}$ = number of CD4 T-cells secreting at least 2 activation markers in the medium conditions

N^{CD4} = Total number of CD4 T-cells involved in the assay (induction of background)

- The Geometric Mean (GM) frequency calculations are performed by taking the anti-log of the mean of the log frequency transformations.
- The CMI vaccine response to gE will be based on the gE-specific data as computed above. The lower limit of linearity (LLL) for the assay (354 positive events/10^6 CD4+ T-cells) will be used as threshold for vaccine response assessment. The vaccine response is defined as the percentage of subjects who have at least a:
  - 2-fold increase as compared to the LLL, for subjects with pre-vaccination gE-specific CD4[2+] T cell frequencies below the LLL.
  - 2-fold increase as compared to pre-vaccination gE-specific CD4[2+] T cell frequencies, for subjects with pre-vaccination gE-specific CD4[2+] T cell frequencies above the LLL.

6.2.6.5. Onset day

The onset day for an event (e.g., AE, concomitant medication/vaccination) is the number of days between the last study dose and the start date of the event. This is 1 for an event occurring on the same day as a study dose (and reported as starting after study dose).

6.2.6.6. Duration of events

The duration of an event with a start and end date will be the difference between the start and end date plus one day, i.e., an event that starts on 3 March 2018 and ends on 12 March 2018 has a duration of 10 days. Duration is 1 day for an event starting and ending on the same day.

The duration of solicited events will be calculated as the sum of the individual days with the AE reported at grade 1 or higher during the solicited event period.

6.2.6.7. Counting rules for combining solicited and unsolicited adverse events

For output combining solicited and unsolicited AEs, all SAEs will be considered general events since the administration site flag is not included in the expedited AE CRF pages. Unsolicited AEs with missing administration site flag will also be considered general.

Multiple events with the same MedDRA PT which start on the same day are counted as only one occurrence.

6.2.6.8. Counting rules for occurrences of solicited events

When the occurrences of solicited events are summarized, each event recorded as having occurred during a specific period will be counted as only one occurrence regardless of the number of days on which it occurs.

6.2.6.9. Grading rule for solicited events

The maximum intensity of local injection site redness/swelling will be scored at GSK as follows:

0	:	< 20 mm diameter
1	:	$\geq$ 20 mm to $\leq$ 50 mm diameter
2	:	> 50 mm to $\leq$100 mm diameter
3	:	> 100 mm diameter

The preferred route for recording temperature in this study is oral. When there is no other alternative, the temperature may be recorded by another route. If the temperature is taken by another route (axillary, rectal or tympanic), the route should be documented. Fever is defined as temperature ≥38.0°C.

6.2.7. Display of decimals

6.2.7.1. Percentages

Percentages and their corresponding confidence limits will be displayed with one decimal except for 100% in which case no decimal will be displayed. Differences in percentages and their corresponding confidence limits will be displayed with two decimals.

6.2.7.2. Demographics and baseline characteristics statistics

The mean, median, and SD for continuous baseline characteristics will be presented with one decimal.

The minimum and maximum values and quartile values (if required) will be presented with the same number of decimals as the observed values.

6.2.7.3. Serological summary statistics

For anti-gE ELISA, geometric mean concentrations (GMC) and their confidence limits will be presented with one decimal, as well as GMC fold increase from pre-dose. GMC ratios and their confidence limits will be displayed with 2 decimals.

7. REFERENCES

Clopper CJ, Pearson E. The Use of Confidence or Fiducial Limits Illustrated in the case of the Binomial. *Biometrika.* 1934;26:404-13.